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A novel intramolecular defluorinative cyclization approach to the synthesis of difluoromethylated quinazolic acid derivatives

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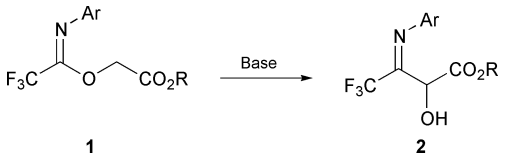
***tert*-Butyl 2-(difluoromethyl)-3-benzyl-6-methoxy-3,4-dihydro-4-quinazoline-4-carboxylic ester (4) and its related 6-substituted esters, precursors of a new type of cyclic amino acid, were synthesized *via* intramolecular defluorinative cyclization under basic conditions.**

The recent achievement of the synthesis of fluorinated isoserines[1] *via* Wittig rearrangement of **1** to **2** in Scheme 1, engaged us in exploration on the synthesis of other new heteroatom-substituted amino acids and their derivatives which are expected to be candidates for biologically important inhibitors.[2] Here, we report the discovery of a novel defluorinative cyclization (**3** → **4**) leading to the synthesis of difluoromethylated quinazolic derivatives.

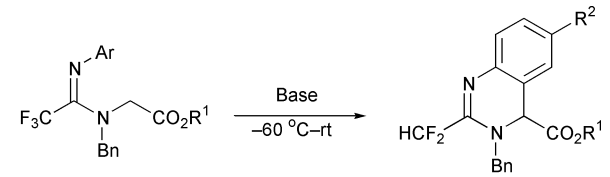


1 **2**

Scheme 1

Difluoromethylated amino acids are known to be important members of the family of fluorinated amino acids.[3] Introduction of difluoromethyl groups into nonfluorinated amino acids[4] or the synthesis of difluoromethyl-substituted amino acids from suitable fluorinated building blocks[5] is a great challenge in synthetic organofluorine chemistry. Selective defluorination from a trifluoromethyl moiety has been widely employed for promising construction of difluoromethylene moiety due to easy availability of trifluoromethyl compounds.[6] The present discovery of defluorinative cyclization of trifluoromethyl-substituted iminoamines **3**[7] provides a novel and efficient approach to the new *N*-heterocyclic *tert*-butyl 2-(difluoromethyl)-3-benzyl-6-methoxy-3,4-dihydro-4-quinazoline-4-carboxylic ester **4**[8] and the related 6-substituted esters (Scheme 2, Table 1), which is otherwise difficult.

The ester **3** was treated with LTMP (1.3 eq.) in THF at −60 °C for 10 min or *n*-BuLi (1.2 eq.) at 0 °C, and then the temperature was raised to 20 °C. The mixture was stirred for several hours (monitored by TLC) or 1 h, respectively.



3 **4**

Ar = 4-MeO-C_6H_4, 4-CH_3-C_6H_4, 3,4-Cl_2-C_6H_3, C_6H_5, Naphthyl

R^1 = *t*-Bu, Me; R^2 = OMe, Me, H.

Base = LTMP or *n*-BuLi LTMP = Lithium tetramethylpiperidide

Scheme 2

A sterically hindered base (LTMP) provided better yield (63%) of **4a** than LDA (47%). In the 3,4-dichloro-substituted iminoamine (entry 7 in Table 1), *n*-BuLi was found to be more useful than LTMP. Both electron-withdrawing and -donating substituents on the aromatic ring affected the formation of **4**. The 2,6-dimethylphenyl compound (entry 9) afforded no corresponding cyclized compound **4** and the starting substrate was recovered.

The quinazolic esters (**4a**–**f**) obtained in the reaction are liquids and their structures were elucidated by spectroscopic and elemental analyses, along with X-ray crystallographic structural analysis of its methyl ester (**4g**),[9] which are colorless needle crystals. Existence of both CHF_2 group and a 1,2,4-trisubstituted benzene ring in **4a** (entry 1 in Table 1, Ar = *p*-methoxyphenyl, R^1 = *t*-Bu) was rationalized by the observation of a doublet at δ = 45.8 ppm (J_{HF} = 53.6 Hz) in ^{19}F NMR (C_6F_6 as an internal standard) and a triplet at δ = 6.33 ppm (J_{HF} = 53.6 Hz) in ^{1}H NMR, and three sets of aromatic protons [δ = 6.52 (d, J = 2.8 Hz), 6.74 (dd, J = 8.7 Hz, 2.8 Hz), and 7.11 ppm (d, J = 8.7 Hz)], respectively.

A mechanism of this reaction is tentatively proposed as shown in Scheme 3.

No Stevens-type rearrangement[9] products **8** were observed although Wittig-type rearrangement is known in fluorinated imino ethers (**1** → **2**).[1] The generation of carbanions **5** by LTMP at lower temperature (−60 °C) was confirmed by the quantitative formation of deuterated product **6** on treating with D_2O. Intramolecular nucleophilic attack of the carbanion onto the imino carbon followed by nucleophilic ring opening of the aziridine type intermediate (**7** → **9**) and simultaneous defluorination would lead to the formation of the quinazoline intermediate **9**, which undergoes base-catalyzed proton migration to the quinazolic products **4**. The rate-determining intramolecular nucleophilic attack *via* intermediate **7** would make the equilibrium (**5** ⇄ **7**) proceed in the forward direction. Thus, the sterically hindered 2,6-dimethyl compound (Table 1, entry 9) was recovered entirely though an α-proton of the carboalkoxy group of **3** (Ar = 2,6-dimethylphenyl) was deuterated by quenching the reaction mixture with D_2O at −60 °C. The preference of path A over path B would arise from the poorer leaving ability of *N*-benzyl anion (Scheme 3) than alkoxide anion in Wittig rearrangement (**1** → **2**).

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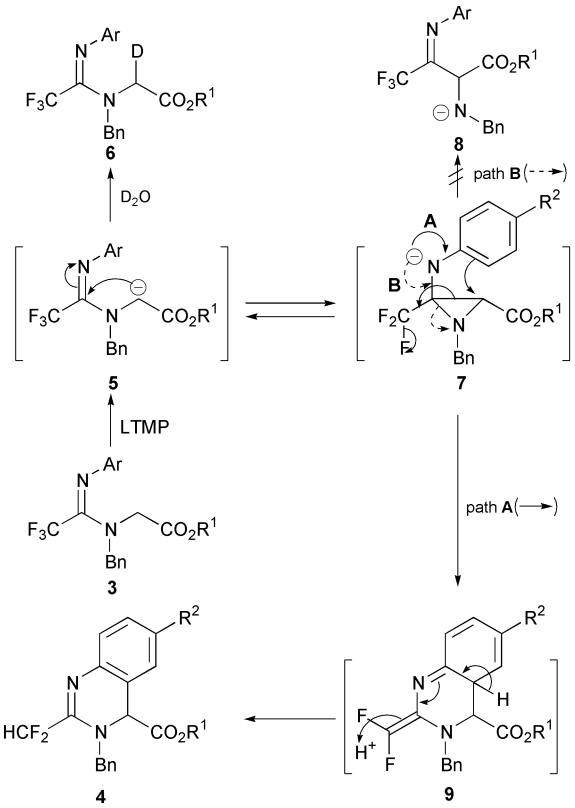
Table 1 Yield of **4** in the base-catalyzed rearrangement of **3**

Entry	Ar	R^1	Base (eq.)	Yield of **4** (%)
1	4-$MeOC_6H_4$	*t*-Bu	LTMP (1.3)	**4a** (63)
2	4-$CH_3C_6H_4$	*t*-Bu	*n*-BuLi (1.2)	**4b** (58)
3	C_6H_5	*t*-Bu	*n*-BuLi (1.2)	**4c** (54)
4	1-Naphthyl	*t*-Bu	LTMP (1.3)	**4d** (80)
5	1-Naphthyl	Me	LTMP (1.3)	**4e** (67)
6	3,4-$Cl_2C_6H_3$	*t*-Bu	LTMP (1.3)	**4f** (78)
7	3,4-$Cl_2C_6H_3$	*t*-Bu	*n*-BuLi (1.2)	**4f** (91)
8	3,4-$Cl_2C_6H_3$	Me	LTMP (1.3)	**4g** (29)
9	2,6-$(CH_3)_2C_6H_3$	*t*-Bu	LTMP (1.3)	Recovery of **3**



Scheme 3

(No 12450356) and the SC-NMR Laboratory of Okayama University for ^{19}F NMR analysis and VBL for X-ray analysis.

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7 The esters **3** were readily prepared by the reaction of *N*-benzyl glycinates with trifluoroacetimidoyl chlorides[11] in good to excellent yields.

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9 $C_{18}H_{14}O_2N_2F_2Cl_2$, M = 399.38, Z = 2, D_{calc} = 1.46, triclinic, a = 8.788(6), b = 13.147(7), c = 8.763(4) Å, α = 96.347(2), β = 113.782(4), γ = 78.837(2)°, U = 908.300 Å^3, T = 288 K, space group $P\bar{1}$ (no. 2), Z = 2, μ(Mo-Kα) = 3.91 cm^{-1}, 2549 reflections measured. The final R was 0.062, R_w was 0.090. CCDC 182/1766. See http://www.rsc.org/suppdata/cc/b0/b005611l/ for crystallographic files in .cif format.

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